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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	PAPER NUMBER
1652	
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08/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,125	PIZZA ET AL.	
	Examiner	Art Unit	
	GANAPATHIRAMA RAGHU	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,9,11 and 14* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/12/08; 05/07/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

In response to the Non-Final Office Action dated 11/07/08, applicants' response filed on 05/07/09 is acknowledged.

Claims 1-7, 9, 11 and 14 are pending, claim 14 remains withdrawn as said claim is directed to nonelected invention, thus claims 1-7, 9 and 11 and are under consideration in the instant Office Action.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 12/12/08 and 05/07/09 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the IDS are considered and initialed by the examiner.

Maintained-Double Patenting rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7, 9 and 11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27, 28, 36, 38, 45 and 46 of Masignani et al., (US Application No.: 10/472,681). An

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claims are not patentably distinct from the reference claims, because the examined claims are either anticipated by, or would have been obvious over reference claims. See, e.g., *In re Berg*, 140 F.3d 1428,46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir.1993); *In re Longi* 759 F.2d 887,225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1-7, 9 and 11 of the instant application are directed to any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. Claims 27, 28, 36, 38, 45 and 46 of the reference application Masignani et al., (US Application No.: 10/472,681) are also directed to an isolated adenosine diphosphate (ADP)-ribosylating protein comprising an amino acid sequence having greater than 80%-95% sequence identity to the amino acid sequence of SEQ ID NO: 1 (the SEQ ID NO: 1 of the reference application has 100% sequence homology to SEQ ID NO: 1 of the instant application), wherein the ADP-ribosylating activity of the polypeptide is reduced or eliminated as compared to the wild-type sequence of SEQ ID NO: 1 (as in claims 27, 45 and 46 of the reference application), said polypeptide further comprising one or more mutations selected from the group of mutations (as in claim 28 of the reference application) such as Glu 109 mutated to Asp (as in SEQ ID NO: 2 of the

instant application, claim 4), Glu 111 mutated to Asp (as in SEQ ID NO: 3 of the instant application, claim 4), Glu 120 mutated to Asp (as in SEQ ID NO: 4 of the instant application, claim 4) and immunogenic compositions comprising the said polypeptide and an antigen (as in claims 36 and 38 of the reference application). The copending claims therefore encompass a genus of polypeptides, which overlaps with the genus of instant claims i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen as recited in claims 1-7, 9 and 11 of the instant application cannot be considered patentably distinct over 27, 28, 36, 38, 45 and 46 of reference application Masignani et al., (US Application No.: 10/472,681), when there is specifically recited embodiment in the copending application which supports the claimed genus, that would anticipate claims 1-7, 9 and 11 of the instant application i. e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. Alternatively, claims 1-7, 9 and 11 of the instant application cannot be considered patentably distinct over claims 27, 28, 36, 38, 45 and 46 of reference application Masignani et al., (US Application No.: 10/472,681) when there is specifically disclosed

embodiment in the reference application of Masignani et al., (US Application No.: 10/472,681) that supports claims 27, 28, 36, 38, 45 and 46 of that application and falls within the scope of the claims 1-7, 9 and 11 herein i. e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen herein, because it would have been obvious to one having ordinary skill in the art to modify claims 27, 28, 36, 38, 45 and 46 of the reference by selecting a specifically disclosed embodiment that supports those claims of the copending application. One of ordinary skill in the art would have been motivated to do this because that embodiment is disclosed as being preferred embodiment within claims 27, 28, 36, 38, 45 and 46 of the reference application of Masignani et al., (US Application No.: 10/472,681).

In response to the above rejection applicants provide the following argument:

"Applicants respectfully request that the examiner hold this rejection in abeyance until such time as there is an indication of otherwise allowable subject matter. Only at that time will the applicants be able to determine whether an obviousness-type double patenting rejection is applicable..." (pages 10-11 of applicants response dated 05/07/09).

Reply: None of the claims are ready to be allowed and therefore the above rejection is maintained.

New-Claim Rejections: 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 (claim 3 dependent thereon) is indefinite in the recitation of "substitution at one or more of amino acids Glu-109, Glu-111 or Glu-120" for the following reasons. The reference to specific positions is unclear and confusing in the absence of the specific sequence to which those positions belong. It is suggested that if the sequence of the *Neissseria menigitidis ADP-ribosylating enzyme* is disclosed in the sequence listing, the corresponding sequence identifier (i.e., SEQ ID NO:X) be used in the claim. For examination purposes, it will be assumed that the claim reads on any "mutant *Neissseria menigitidis ADP-ribosylating enzyme*" of undefined structure and function. Correction is required.

Maintained-Claim Rejections: 35 USC § 112-Second Paragraph

Claims 1-3 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the phrase "A mutant *Neisseria meningitides* ADP-ribosylating enzyme…", it is not clear to the examiner as to what this phrase means in the context of the above claims. It is not clear what biological or structural or chemical or functional elements/features must be encompassed. How many changes to SEQ ID NO:1 can be present and still be a mutant *Neisseria meningitides* ADP-ribosylating enzyme?. Examiner suggests applicants to make a direct reference to specific SEQ ID NO:. Clarification and correction is required.

Previous rejection of claims 1-3 and 11 under 35 U.S.C. 112, second paragraph be withdrawn, applicants' provide the following arguments.

"The claim distinctly points out and claims a mutant *Neisseria meningitides* ADP-ribosylating enzyme with a substitution at one or more amino acids Glu-109, Glu-111 or Glu-120... ADP-ribosylating enzymes are a well documented class of bacterial toxins that, despite lacking primary sequence homology, exhibit a highly conserved catalytic domain that serves as the NAD-binding cavity and acts as a unique molecular signature for this class of enzymes...Examiner also questions how many changes to SEQ ID NO: 1 can be present and still be mutant *Neisseria meningitides* ADP-ribosylating enzyme. This question is not relevant to the pending claims since the claims specify the nature of the mutation which is substitution at one of the three recited residues..." (pages 2-3 of applicants response dated 05/07/09).

Reply: Applicant's arguments filed on 05/07/09 have been fully considered but they are not persuasive for the following reasons:

1) The specification and art describes the structure of a single *Neisseria meningitides* ADP-ribosylating enzyme. However, there is yet a possibility that many other unknown alleles in many different strains of *Neisseria meningitides* that have similar or identical functions as ADP-ribosylating enzyme like and exhibiting a highly conserved catalytic domain that serves as the NAD-binding cavity with unique molecular signature, said signatures not corresponding to Glu-109, Glu-111 or Glu-120 could be potentially discovered and described. Thus, structure correlating to function is required if specific codon positions are recited in the claims to enable a skilled artisan to

understand which specific structure is being referred to in the claims, and as such, the recitation of specific positions without a sequence identifier associated to those positions is unclear and confusing, because the codon recited may well be different from the one applicants intend to encompass.

2) The art teaches several examples annotated as ADP-ribosylating enzyme with disparate structures (see enclosed printout from PubMed, 340 structures are known), i.e., lack of primary structure homology (Domenighini et al., Mol. Microbiol., 1994, Vol. 14 (1): 41-50, in IDS). In parallel, the art also teaches, proteins having similar structure have different activities (structure does not always correlate to function); Witkowski et al., (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Similarly, i) Wishart et al., (J. Biol. Chem., 1995, Vol. 270(10): 26782-26785) teach that a single mutation converts a novel phosphotyrosine binding domain into a dual-specificity phosphatase and ii) Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art also teaches that functionally similar molecules have different structures; Kisselev L., (Structure, 2002, Vol. 10: 8-9) teach that polypeptide release factors in prokaryotes and eukaryotes have same function but different structures. It is also noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry, 1999, Vol. 38: 11643-116150) teaches that

one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol., 2001, Vol. 183 (8): 2405-2410) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function.

Given this scenario, a skilled artisan needs to be provided with the structure of parent sequence i.e., the claims should point out and distinctly claim the subject matter which applicant regards as the invention, especially one of the preferred embodiments of the claimed mutant *Neisseria meningitides* ADP-ribosylating enzyme is as an immunogen; therefore the question arises "what biological or structural or chemical or functional elements/features must be encompassed? and how many changes to SEQ ID NO: 1 can be present and still be mutant *Neisseria meningitides* ADP-ribosylating enzyme with the desired properties?".

Maintained-Claim Rejections: 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Maintained-Enablement

Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 2, 3 or 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-

type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D), does not reasonably provide enablement for any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claim.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-3, 5-7, 9 and 11 are so broad as to encompass for any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and

use of said mutant as an immunogen. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. In this case the disclosure is limited to an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D). In view of the great breadth of the claims, the amount of experimentation required to determine a use for the full scope of the claims, i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein

comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340). In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompasses any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. The specification does

not enable the full scope of claims 1-3, 5-7, 9 and 11, because the specification does not establish: **(A)** mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, the structure of all polypeptides with desired activity i.e., reduced or eliminated ADP-ribosyltransferase activity and as an immunogen; **(B)** the general tolerance of the polypeptide to modification and extent of such tolerance; **(C)** a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and **(D)** the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides and encoding polypeptides with an enormous number of modifications. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to

one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request that said rejection be withdrawn, applicants' provide the following arguments:

(A) "...The examiner alleges that because claimed invention is open-ended and would cover other mutations in the enzyme outside of the substitution mutations ...as stated above, such other mutations are irrelevant to the scope of the claims since their presence or absence do not affect whether the enzyme is within the scope of the claims, all that matters is whether there is a substitution at one of the three specified residues.... The applicants work demonstrating that substitution at the Glu-109, Glu-111 or Glu-120 are sufficient to inactivate the toxic activity and therefore one skill in the art would appreciate that any *Neisseria meningitides* ADP-ribosylating enzyme mutant with a substitution at the Glu-109, Glu-111 or Glu-120 would inactivate the toxic activity. Finally, as long as the *Neisseria meningitides* ADP-ribosylating enzyme has such a substitution meeting the claim limitation, the mutant will not have toxic activity regardless of any other additional mutations generated elsewhere in the enzyme (page 4 of applicants response dated 05/07/09).

(B) Additionally, the claims are not drawn to any and all *Neisseria meningitides* ADP-ribosylating mutant proteins that function for any purpose but rather require that the mutant protein have a substitution at one or more of amino acids Glu-109, or Glu-

111 or Glu-120 which are well known catalytic sites...Further, the specification must be viewed in the light of information known in the art (page 5 of applicants response dated 05/07/09).

(C) Applicants submit that there is ample guidance provided in the specification and that undue experimentation is not required to practice the claimed invention...Further, the examiner did not in any way establish unpredictability (pages 7-8 of applicants response dated 05/07/09).

Reply: (A), (B) & (C): Applicant's arguments filed on 05/07/09 have been fully considered but they are not persuasive. The scope of these claims are broad despite the guidance of the art and specification, the claims remain not commensurate in scope with the enabled invention. Examiner finds support for his position in the following scientific teachings:

1) The specification and art describes the structure of a single *Neisseria meningitides* ADP-ribosylating enzyme. However, there is yet a possibility that many other unknown alleles in many different strains of *Neisseria meningitides* that have similar or identical functions as ADP-ribosylating enzyme like and exhibiting a highly conserved catalytic domain that serves as the NAD-binding cavity with unique molecular signature, said signatures not corresponding to Glu-109, Glu-111 or Glu-120 could be potentially discovered and described. Thus, structure correlating to function is required if specific codon positions are recited in the claims to enable a skilled artisan to understand which specific structure is being referred to in the claims, and as such, the recitation of specific positions without a sequence identifier associated to those

positions is unclear and confusing, because the codon recited may well be different from the one applicants intend to encompass.

2) The art teaches several examples annotated as ADP-ribosylating enzyme with disparate structures (see enclosed printout from PubMed, 340 structures are known), i.e., lack of primary structure homology (Domenighini et al., Mol. Microbiol., 1994, Vol. 14 (1): 41-50, in IDS). In parallel, the art also teaches, proteins having similar structure have different activities (structure does not always correlate to function); Witkowski et al., (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Similarly, i) Wishart et al., (J. Biol. Chem., 1995, Vol. 270(10): 26782-26785) teach that a single mutation converts a novel phosphotyrosine binding domain into a dual-specificity phosphatase and ii) Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art also teaches that functionally similar molecules have different structures; Kisselev L., (Structure, 2002, Vol. 10: 8-9) teach that polypeptide release factors in prokaryotes and eukaryotes have same function but different structures. It is also noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry, 1999, Vol. 38: 11643-116150) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity.

Seffernick et al. (J. Bacteriol., 2001, Vol. 183 (8): 2405-2410) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function.

Given this scenario, a skilled artisan needs to be provided with the structure of parent sequence i.e., the claims should point out and distinctly claim the subject matter which applicant regards as the invention, especially one of the preferred embodiments of the claimed mutant *Neisseria meningitides* ADP-ribosylating enzyme is as an immunogen; therefore the question arises "what biological or structural or chemical or functional elements/features must be encompassed? and how many changes to SEQ ID NO: 1 can be present and still be mutant *Neisseria meningitides* ADP-ribosylating enzyme with the desired properties?".

Therefore, examiner would like to point out that none of the claims as written recite any limitation regarding increased immunogenecity and only claim 2 recites reduced or eliminated catalytic activity and therefore examiner continues to hold the position that applicants' have construed that the amendments to claims limits the claims only to what is disclosed in the specification and the crux of the applicants' argument is based on this conception i. e., the mutation encompasses only the catalytic residues of Glu-109, Glu-111 or Glu-120 of SEQ ID NO: 1. However, examiner would like to reiterate that the conception/belief of the applicant is not correct. Amended claims as written when given the broadest reasonable interpretation reads on any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any

substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen i.e., any random mutants of SEQ ID NO: 1 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. Furthermore, examiner has never taken the position that other mutations at positions 109, 111 and 120 are not enabled, however inclusion of one or more of these said mutations within any mutant ADP-ribosylating enzyme is not enabled.

Furthermore, the specification only discloses three specific mutants (SEQ ID NO: 2, 3 & 4) comprising the full-length sequence of SEQ ID NO: 1 having reduced or eliminated ADP ribosyltransferase and or NAD-glycohydrolase activity as compared to the wild-type enzyme and said mutants to be immunogenic. However, the specification has not provided structure-function correlationship (reduced catalytic activity or increased immunogenecity or able to elicit protective antibodies) i. e., any other random mutant of SEQ ID NO:1 or any other fragment of SEQ ID NO: 1 of any length wherein said fragment includes one or more amino acids Glu-109, Glu-11 or Glu-120 or said residues substituted with any other residue in said ribosylating protein and being immunogenic. For argument sake, even if a skilled artisan is required to generate a mutant/variant *Neisseria meningitides* ADP-ribosylating enzyme the applicants' are referring to, said *Neisseria meningitides* ADP-ribosylating enzyme having 145 amino

acid residues, in theory a skilled artisan would be compelled to generate the following number of possible variants/mutants and is represented by the formula [n!] X 19^a where n is the length of the polypeptide and "a" is the number of substitutions to be made. Again for argument sake if the number of substitution is at a single amino acid codon (i.e., a single substitution) and there are 19 other possible amino acids that can be substituted at any given position, the number of possible variants that can be generated for *Neisseria meningitides* ADP-ribosylating enzyme having 145 amino acid residues is [145!] X 19 = 1.5 X 10^{253}. Therefore, the specification does not provide support for the full scope and breadth of the claims even following the amendments to claims and examiner continues to hold the position the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue.

Therefore, examiner takes the position that due to the paucity of information regarding structure-function correlation, the specification lacks identifying characteristics of all of the sequences within the claimed genus, especially; of any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen (for claims interpretation also see 112, second paragraph rejection). Thus, random variants and mutants of *Neisseria meningitides* ADP-ribosylating enzyme, as the parent structure (sequence identifier) is not defined, would clearly constitute **undue** experimentation.

The broadest interpretation of claims encompasses a genus of *Neisseria meningitides* ADP-ribosylating enzyme of undefined structure and their variants with any structure and clearly constitutes undue experimentation as it would involve making and testing many sequences including the mutants, variants and recombinants of said parent sequences.

Claims are given the broadest interpretation and under this interpretation when there are no defined structural features or a reference to a parent sequence, the modified/variant *Neisseria meningitides* ADP-ribosylating enzyme can potentially have any number of structural features with no correlation to structure-function i.e., desired biological characteristics.

Examiner would like to reiterate that to determine the effect of structural modification on the *Neisseria meningitides* ADP-ribosylating enzyme, a skilled artisan should be provided with details and guidance regarding the how the structure of any *Neisseria meningitides* ADP-ribosylating enzyme or a variant thereof is correlated with its activity i.e., desired biological characteristics. The specification is limited to the guidance provided for an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 2, 3 or 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D).

For these reasons, claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph for enablement as the scope and breadth of the claims encompasses

many *Neisseria meningitides* ADP-ribosylating enzyme with different structures lacking correlated function and hence, the guidance provided by the art or the specification is in-sufficient, determination of *Neisseria meningitides* ADP-ribosylating enzyme having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and ***undue.***

Maintained-Written Description

Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-3, 5-7, 9 and 11, as interpreted, are directed to a genus of polypeptides i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in

possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, there is no structure correlated to associated function (undefined biological or structural or chemical or functional elements/features are encompassed, see 112 second paragraph rejection) recited in claims with regard to the members of the genus polypeptides i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. While the specification in the instant application discloses the structure; an isolated mutant *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 2, 3 or 4 having reduced or eliminated ADP-ribosyltransferase activity and as an immunogen as compared to wild-type *Neisseria meningitides* ADP-ribosylating enzyme of SEQ ID NO: 1, wherein said mutant enzyme has a substitution of Glu (E)-120 to Asp (D), it fails to provide any information as to the structure associated with function for the genus of polypeptides claimed i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more

amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen, with no structural limitations. The lack of description of any additional mutants from any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that applicants' were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In support of their request that said rejection be withdrawn, applicants' have provided the following argument.

(A) Examiner has not established a prima facie case of failure to comply with written description requirement..." (page 8 of applicants response dated 05/07/09).

(B) Examiner has remained silent on two recent cases from the Federal Circuit on two cases...Both of these cases make clear that the case cited by the examiner *Eli Lilly*, only applies to new genes in entirely new functional classes... (page 9 of applicants response dated 05/07/09).

However, examiner maintains the rejection and the reason for the examiner's position is given below.

Reply (A) & (B):

1) The specification and art describes the structure of a single *Neisseria meningitides* ADP-ribosylating enzyme. However, there is yet a possibility that many other unknown alleles in many different strains of *Neisseria meningitides* that have similar or identical functions as ADP-ribosylating enzyme like and exhibiting a highly conserved catalytic domain that serves as the NAD-binding cavity with unique molecular signature, said signatures not corresponding to Glu-109, Glu-111 or Glu-120 could be potentially discovered and described. Thus, structure correlating to function is required if specific codon positions are recited in the claims to enable a skilled artisan to understand which specific structure is being referred to in the claims, and as such, the recitation of specific positions without a sequence identifier associated to those positions is unclear and confusing, because the codon recited may well be different from the one applicants intend to encompass.

2) The art teaches several examples annotated as ADP-ribosylating enzyme with disparate structures (see enclosed printout from PubMed, 340 structures are known), i.e., lack of primary structure homology (Domenighini et al., Mol. Microbiol., 1994, Vol. 14 (1): 41-50, in IDS). In parallel, the art also teaches, proteins having similar structure have different activities (structure does not always correlate to function); Witkowski et al., (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Similarly, i) Wishart et al., (J. Biol. Chem., 1995, Vol. 270(10): 26782-26785) teach that a single mutation converts a novel

phosphotyrosine binding domain into a dual-specificity phosphatase and ii) Broun et al., (Science 282:1315-1317, 1998), teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art also teaches that functionally similar molecules have different structures; Kisselev L., (Structure, 2002, Vol. 10: 8-9) teach that polypeptide release factors in prokaryotes and eukaryotes have same function but different structures. It is also noted that the art teaches several examples of how even small changes in structure can lead to changes in function. For example, Witkowski et al. (Biochemistry, 1999, Vol. 38: 11643-116150) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol., 2001, Vol. 183 (8): 2405-2410) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function.

Given this scenario, a skilled artisan needs to be provided with the structure of parent sequence i.e., the claims should point out and distinctly claim the subject matter which applicant regards as the invention, especially one of the preferred embodiments of the claimed mutant *Neisseria meningitides* ADP-ribosylating enzyme is as an immunogen; therefore the question arises "what biological or structural or chemical or functional elements/features must be encompassed? and how many changes to SEQ

ID NO: 1 can be present and still be mutant *Neisseria meningitides* ADP-ribosylating enzyme with the desired properties?".

Therefore, the arguments presented by the examiner in sustaining the enablement rejection equally applies to written-description and therefore applicants' arguments are not persuasive because claims as written are not limited to only the catalytic residues of Glu-109, Glu-111 or Glu-120 of SEQ ID NO: 1 and as indicated above in the enablement rejection, claims when given the broadest reasonable interpretation read on any mutant *Neisseria meningitides* ADP-ribosylating enzyme wherein said mutant enzyme has any substitution in SEQ ID NO: 1 including one or more amino acids Glu-109 or Glu-111 or Glu-120 or any protein comprising a fragment of said ADP-ribosylating enzyme that includes any substitution to one or more amino acids Glu-109, Glu-111 or Glu-120 and use of said mutant as an immunogen. Based on this interpretation and lack of description of any additional mutants and their structure-function correlationship i.e., any mutant *Neisseria meningitides* ADP-ribosylating enzyme or any protein comprising fragments of said mutant wherein said polypeptides or the fragments of said polypeptides have reduced or eliminated ADP ribosyltransferase and use of said mutants as an immunogen (eliciting protective antibodies) by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that applicants' were in possession of the claimed invention.

Examiner continues to hold the position that, the genus of polypeptides and encoding polynucleotides as recited in the claimed invention is an extremely large and

structurally variable genus. Therefore, the claimed genera of polypeptides and encoding polynucleotides include peptides having widely variable structures, since minor structural changes may result in changes affecting function and no additional information correlating structure with function has been provided.

Many structurally unrelated polynucleotides and encoded polypeptides are encompassed by these claims. The specification only discloses a single species within the recited genus, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the required genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

As argued by the examiner above in the enablement rejection, the genus of polypeptides required in the claimed invention is extremely large and structurally variable genus. Therefore, claims as written lack structure-function correlationship and as taught by the art there is considerable structural diversity within the generally stated functions such as ADP-ribosylating enzyme. Structure correlated with function is necessary, as supported by scientific evidence that even minor changes in structure may result in drastic changes in function.

Thus, the instant claims would encompass many different structures and functions and a parent sequence/structure correlated with requisite function should be defined, in the absence of such information further testing of the variants and mutants would be required by the skilled artisan. Based on the lack of knowledge and predictability in the art (see scientific evidence above), amended claims as written would

encompass any *Neisseria meningitides* ADP-ribosylating enzyme that are structurally divergent with concomitant change in the function. For these reasons, claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph for written description.

Furthermore; 1) The key focus of the argument is on the claims as written (see *In re Hinkler* 150 F .3d 1362, 1369, 47 USPQ2d 1523 (fed. Cir. 1998) and not proffered facts and are not commensurate with the scope of claims and therefore unpersuasive.

2) Although the claims are examined in the light of the specification, specification cannot be read into the claims, i.e., the limitations of the specification cannot be read into the claims (see MPEP 2111 R-5).

415 F.3d at 1316, 75 USPQ2d at 1329. See also< In re Hyatt, 211 F.3d 1367, 1372,54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969) (Claim 9 was directed to a process of analyzing data generated by mass spectrographic analysis of a gas. The process comprised selecting the data to be analyzed by subjecting the data to a mathematical manipulation. The examiner made rejections under 35 U.S.C. 101 and 102. In the 35 U.S.C. 102 rejection, the examiner explained that the claim was anticipated by a mental process augmented by pencil and paper markings. The court agreed that the claim was not limited to using a machine to carry out the process since the claim did not explicitly set forth the machine. The court explained that "reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from reading limitations of the specification into a claim,' to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim." The court found that applicant was advocating the latter, i.e., the impermissible importation of subject matter from the specification into the claim.). See also In re Morris, 127 F.3d 1048, 1054-55, 44 USPQ2d 1023, 1027-28 (Fed. Cir. 1997) (The court held that the PTO is not required, in the course of prosecution, to interpret claims in applications in the same manner as a court would interpret claims in an infringement suit. Rather, the "PTO applies to verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in applicant's specification."). The broadest reasonable interpretation of the claims must also be consistent with the interpretation that those skilled in the art would reach.

For the above cited reasons, claims 1-3, 5-7, 9 and 11 rejected under 35 U.S.C. 112, first paragraph for enablement and written description is maintained.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1) Claims 1-7, 9 and 11 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27, 28, 36, 38, 45 and 46 of Masignani et al., (US Application No.: 10/472,681).

2) Claims 1-3 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

3) Claims 1-3, 5-7, 9 and 11 are rejected under 35 U.S.C. 112, first paragraph, for enablement and written description.

Conclusion

None of the claims are allowable. Claims 1-7, 9 and 11 are rejected for the reasons identified in the Rejections and Summary sections of this Office Action. Applicants must respond to the rejections in each of the sections in this Office Action to be fully responsive for prosecution.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for

the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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